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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,819	01/17/2001	Christopher J. Stanley	PM 275510 P5642US	5588

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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	6

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	Stanley, C.	
	Examiner	Art Unit	
	Frank Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2002* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on June 4, 2002 has been entered as Paper No: 5. The claims pending in this application are claims 1-22. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Claim Objections

2. Claims 7-9, 11-13, 15, and 16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend from another multiple dependent claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Note claim 20 is dependent on claim 18 while claim 22 is dependent on claim 21.

Note the specification does not adequately describe " a carrier macromolecule that does not inhibit DNA polymerase activity" as recited in independent claims 1, 18, and 21. MPEP 2163.06 states that "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." In view of the embodiments adequately description in the specification, the subject application does not reasonably convey to one skilled in the art that applicant was in possession of the full scopes of products encompass in the claims at the time of the application was filled. Therefore, the written description requirement has not been satisfied.

In support of this position, attention is directed to the decision of *Vas-Cath inc. V. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 U.S.C. 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Claim Rejections - 35 USC § 102/103

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 21 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Belyavsky *et al.,* (US Patent No. 5,814,445, filed on July 11, 1995) .

Regarding claim 21, for cloning of the differentially expressed sequences (a cDNA fragment), the corresponding bands of gel (containing a DNA fragment) were cut apart and eluted from the gel. Then the fragments was precipitated with three volumes of 96% ethanol using glycogen as carrier. Although Belyavsky *et al.,* did not directly show that glycogen (macromolecule) was bound to a solid support as recited in claim 21, in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Belyavsky *et al.,* since it was known that a complex of the DNA fragment and glycogen was pelleted on the bottom of a centrifuge tube (considered as a solid support) during the precipitation process.

Response to Arguments

In page 7, last paragraph bridging to page 8, first paragraph of applicant's remarks, applicant argued that "centrifuge tubes are generally designed to be inert to avid bonding to the materials introduced to the tubes." since "physically pelleting DNA and glycogen in a glass tube is not a bonding process.".

This arguments has been fully considered but it is not persuasive toward the withdrawal of the rejection. In response to applicant's argument that the reference failed to show certain features of applicant's invention, it was noted that the features upon which applicant relied (i.e., bonding a nucleic acid to carrier macromolecule) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

8. Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lee *et al.,* (BioTechniques, 14, 191 and 192, 1993).

Lee *et al.,* teach DNA sequencing of biotinylated single-stranded DNAs bound to Dynabeads (see pages 191 and 192). Note that: (1) The biotin molecule and the bead here were considered as a carrier macromolecule and a solid support respectively as recited in claims 21 and 22; (2) biotinylated single-stranded DNAs immobilized on Dynabeads could be considered as an immobilized nucleic acid as recited in claims 21 and 22; and (3) although Lee *et al.,* did

not directly to use the biotinylated single-stranded DNAs as a primer or probe as recited in claim 22, in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Lee *et al.,* since the method as recited in claim 22 did not have a hybridization or an amplification step (considered as an intended use).

9. Claims 1, 3, 4, 6, 8, 15, 18, 19, and 21 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Conrad (US Patent No. 5,652,099, filed on August 18, 1994).

Regarding claims 1, 3, 4, 6, 8, 15, 18, 19, and 21, as shown in Example 4, a poly (AC) template was amplified using the biotinylated synthetic 22-mer primers as recited in claim 8. The hybridization between biotinylated poly (AC) and fluorescence-labeled poly (FC) probe produced from the synthetic template poly (TG) were detected by quenched fluorescence of the poly (FC) probe. The hybrids could be adsorbed via the biotin moiety to avidinylated beads (see columns 26 and 27). Note that: (1) biotin could be considered as a carrier macromolecule that did not inhibit DNA polymerase activity, an agarose derivative or cellulose derivative, and a detectable marker as recited in claims 1, 3, 15, 18, and 21; (2) although Conrad did not directly teach to label the primer with biotin (bonding a primer to a carrier macromolecule as recited in claim 1), in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Conrad since the biotin labeled primer was made before the amplification assay; (3) biotin molecule could be considered as water soluble, substantially linear and substantially uncharged at pH from 4 to 10 as recited in claims 4 and 6; (4) the hybridization

between biotinylated poly (AC) (a first nucleic acid) and fluorescence-labeled poly (FC) probe (a second nucleic acid) could be considered to meet the limitations as recited in claims 18 and 19 since biotin and fluorescence dye could be considered as the first and second carrier macromolecules respectively; and (5) the hybrids of biotinylated poly (AC) and fluorescence-labeled poly (FC) probe immobilized on avidinylated beads could be considered to meet the limitations as recited in claim 21 since avidinylated beads could be considered as a solid support and the hybrids could be used as a nucleic acid bound to a carrier macromolecule (biotin).

Response to Arguments

In page 11, last paragraph bridging to page 8, second paragraph of applicant's remarks, applicant argued that: (1) "biotin has a molecular weight of only 224, which is not sufficient for delineating biotin as macromolecule."; (2) Conrad did teach "a nucleic acid primer bound to a carrier macromolecule that does not inhibit DNA polymerase activity, the carrier macromolecule itself being bound to a solid support."; and (3) Conrad "does not disclose a process for the replication of a nucleic acid template, the process comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule that does not inhibit DNA polymerase activity; hybridizing the bound primer to said template; and then extending said primer to replicate said template in a complementary form.".

These arguments has been fully considered but they are not persuasive toward the withdrawal of the rejection. First, even "biotin has a molecular weight of only 224" , biotin could be considered as a macromolecule since the examiner could not found the definition for macromolecule in specification and the molecular weight of biotin was large enough to be called

as a macromolecule. Second, Conrad did teach "a nucleic acid primer bound to a carrier macromolecule that does not inhibit DNA polymerase activity" and "the carrier macromolecule itself being bound to a solid support." (see above rejection). Third, Conrad did disclose a process for the replication of a nucleic acid template comprising hybridizing the bound primer to said template and extending said primer to replicate said template in a complementary form since the process argued by applicant was annealing and extending steps in PCR and was inherent to the reference taught by Conrad.

10. Claims 1-6, 10, 12, 14, 15, 17, 21, and 22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Landegren *et al.,* (US Patent No.4,988,617, published on January 29, 1991).

Regarding claims 1-6, 10, 14, and 15, Landegren *et al.,* teach method of detecting a nucleotide change in nucleic acids. This method comprised following steps: (a) annealing a labeled oligonucleotide target probe of predetermined sequence (considered as the primer as recited in claim 1) to a first sequence of a test substance so that said target nucleotide position was aligned with a nucleotide in an end region of the target probe (considered as a nucleic acid template as recited in claim 1); (b) annealing a labeled adjacent oligonucleotide probe of predetermined sequence (considered as further primer as recited in claims 10 and 14) to a second sequence of said test substance contiguous to said first test substance sequence, so that the end region of said target probe was directly adjacent to said adjacent probe; (c) contacting said annealed target and adjacent probes with a linking agent such as ligase under conditions such that

the directly adjacent ends of said probes will link to form a linked probe product unless there was nucleotide base pair mismatch between the target probe and test substance at the target nucleotide position; (d) separating said test substance from said annealed probes, and (e) detecting whether or not linking occurs as an indication of nucleotide base pair matching or mismatching at said target nucleotide position. These labels on oligonucleotide target and adjacent probes could be radioactive tags, enzymes, fluorescent tags, and colorimetric tags (see Figure 1 and columns 2-4, 8, and 9). Note that: (1) the label such as fluorescent tags on the oligonucleotide target probe and the adjacent oligonucleotide probe was considered as a carrier macromolecule that did not inhibit DNA polymerase activity as recited in claim 1 and a detectable marker as recited in claim 15; (2) the label such as enzyme on the oligonucleotide target probe and the adjacent oligonucleotide probe was considered as a carrier macromolecule that did not inhibit DNA polymerase activity as recited in claim 2; (3) although Landegren *et al.*, did not directly teach to label the primer with a tag such as fluorescence dye (bonding a primer to a carrier macromolecule as recited in claim 1), in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Landegren *et al.*, since the primer labeled with a tag such as fluorescence dye was made before a ligation assay; (4) a tag such as fluorescence dye molecule could be considered as water soluble, substantially linear and substantially uncharged at pH from 4 to 10 as recited in claims 4 and 6; and (5) a tag such as enzyme could be considered to have a molecular weight in the range of 1,000 to 40,000,000 as recited in claim 5 since a enzyme with 10 amino acids had a molecular weight of about 1100 (average of molecular weight for an amino acid was 110).

Regarding claims 12, 21, and 22, the oligonucleotide target probe or the adjacent oligonucleotide probe labeled with a tag (carrier macromolecule) could be immobilized on a solid support prior to the ligation assay (see columns 11 and 12). This immobilized oligonucleotide probe labeled with a tag was used in a ligation reaction as recited in claims 21 and 22.

Regrading claim 17, a biological sample could be from human (see column 13).

11. Claims 1, 3, 4, 6, 8, 15, and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Debre *et al.,* (French Patent No. 2, 711, 671, published on May 5, 1995).

Debre *et al.,* teach *in situ* PCR. In this method, Jurkat and peripheral human blood cells were permeabilized and fixed in *in situ* and PCR and reverse transcription PCR were successfully carried out in these cells using fluorescence-labeled primers as recited in claims 1, 8, and 16 (see abstract). Note that: (1) fluorescence could be considered as a carrier macromolecule that did not inhibit DNA polymerase activity, an agarose derivative or cellulose derivative, and a detectable marker as recited in claims 1, 3, and 15; (2) although Debre *et al.*, did not directly teach to label the primer with fluorescence (bonding a primer to a carrier macromolecule as recited in claim 1), in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Debre *et al.,* since the fluorescence labeled primer was made before the amplification assay; and (3) fluorescence molecule could be considered as water

soluble, substantially linear and substantially uncharged at pH from 4 to 10 as recited in claims 4 and 6.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,207,385B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

claims in this instant application and U.S. Patent No. 6,207,385B1 are directed to detecting the presence of a nucleic acid and replicating a nucleic acid template. Note that independent claims 1 and 18 in this instant application are much broader than independent claims 1 and 2 in U.S. Patent No. 6,207,385B1 while dependent claims 2-5, 7-11, and 13-17 in this instant application have only slight differences from dependent claims 3-15 in U.S. Patent No. 6,207,385B1.

Response to Arguments

In page 13, second paragraph of applicant's remarks, applicant stated that "[U]pon receiving indication that the claims are allowable, Applicant will file a terminal disclaimer, if necessary.".

Applicant's request has been fully considered. However, since applicant did not file a terminal disclaimer in response to previous office action, the rejection remained.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
August 2, 2002

ETHAN C. WHISENANT
PRIMARY EXAMINER